Before making any conclusions from these experiments it should be noted that all of the animals except Nos. 18, 19, and 21 had had previous injections of cocaine. The possibility of a slight immunity having been established should be considered. Three out of the seven adrenalin cocaine animals died while none of the control animals died.

What then are the conclusions to be drawn? The same criticism holds here that Braun made of Thies' work. The experiments are made with too large doses of cocaine to show the real value of adrenalin cocaine as a local anæsthetic. What is certainly shown is that *adrenalin will not protect the organism against toxic doses of cocaine.*

In the use of adrenalin cocaine care should be exercised not to inject a toxic dose of the latter, for not only does the adrenalin fail to protect the body against the toxic doses of cocaine, but it seems to enhance the toxic action.

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THE INFLUENZA BACILLUS IN BRONCHIECTASIS.

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THAT dilatation of the bronchi may occur in the course of acute influenza, either of the bronchial or pneumonic type, has been demonstrated by necropsy findings and the cultivation of the specific organism from the lesions. (Leichenstern, M. Beck, and others.) Similar cases have also been reported in which recovery from the acute illness occurred with the gradual development of chronic bronchitis or bronchiectasis.

In our own country the relationship of bacillus influenzæ to chronic pulmonary disease has received but little attention, if we except the extensive investigations of Lord.

It may therefore be of interest to present the findings in some cases observed at the Johns Hopkins Hospital (service of Prof. Osler) during the early part of 1905.

CASE I. *Total duration three months; onset with symptoms of acute coryza; gradual development of cough and profuse expectoration; small hemorrhages, irregular temperature, sweats; influenza bacilli in pure culture from sputum; headache, partial paralysis; death; autopsy; diffuse bronchiectasis, bronchial erosion, patches of bronchopneumonia, small foci of necrosis; influenza bacilli in pure culture from tissues; no tuberculosis.*—B. R. F., male, white, aged twenty-nine years, trained nurse. Admitted February 16, 1905, complaining of "cough and pains in chest."

Family History. Good; negative for tuberculosis.

Past History. No acute diseases of childhood; never any pneumonia; no typhoid fever; no hemoptysis; severe la grippe three years ago; lasted two months; no other pulmonary trouble until present illness; no history of gastric or intestinal disease; no renal troubles; primary syphilitic sore five years ago; no secondaries; always strong and healthy; moderate use of alcohol; heavy smoker of cigarettes; average weight 145 pounds.

Present Illness. Two months before admission patient caught cold after exposure. This was at first slight, not accompanied by cough. It slowly grew worse, however, and there has been severe cough with increasingly profuse expectoration; for about three weeks patient has felt feverish at night. In past four days the cough much worse, with nocturnal dyspnœa, fever, sweats, and pain in right side. He has lost fifteen pounds in weight since onset.

Physical Examination. On admission patient was well nourished and not in great distress. Diminished expansion more marked on right side. Vocal fremitus impaired, with dulness on percussion over right axilla and lower back and over left lower back. Breath sounds enfeebled over dull areas, though nowhere absent. No tubular breathing. No friction rub. No movable dulness. Very numerous moist and sonorous rales over entire chest. Heart sounds clear and of normal relative intensity. Abdomen normal; deep reflexes normal. Temperature irregular, varying in first twenty-four hours from normal to 100.5°. Pulse soft, regular, 96 to minute. No marked thickening of vessel walls. Sputum profuse, greenish, mucopurulent, with a sickening, sweetish odor. Examination for elastic tissue and tubercle bacilli negative. Exploration of chest with needle yielded no results. Leukocytes on admission, 22,000; hæmoglobin, 90 per cent. Patient did not improve, paroxysms of coughing grew worse.

February 24th. First culture from sputum absolutely pure growth of bacillus influenzæ.

25th. Small hemorrhage from lungs, followed by chill and sweat. Pulmonary signs remained about as at first, except for increase in sonorous rales. Leukocytes varied between 12,000 and 25,000.

March 8th. Patient complained of numbness and some apparent weakness in right hand. Some headache. Two days later pain in right testicle, with increased weakness of wrist and muscles of leg on same side; no absolute paralysis, but marked wrist-drop and great weakness of whole right side. No changes in sensation. Testicle objectively normal. Severe and constant headache. No irregularity of pupils. No stiffness of neck. No Kernig's sign. The patient gradually became weaker. On March 18th became very cyanotic and seemed unable to clear the lungs of the accumulated sputum. Signs in the chest were unchanged, except for the increase of loud bubbling rales.

19*th*. Blood cultures on various media entirely sterile. Patient died March 20th. Clinical diagnosis: bronchiectasis.

Autopsy. Both pleural cavities partly obliterated by old adhesions, mostly posterior. Lungs voluminous; surface roughened by fresh fibrinous exudate. On section the lung is foul smelling and studded throughout with irregular patches, which are prominent and rough on cut surface. These patches have usually a yellowish-white centre, surrounded by grayish-red areas. At one point in upper right lobe there is a small cavity with a necrotic lining and surrounded by an area of consolidation.

The bronchi are dilated and contain a considerable quantity of a thick, semi-fluid material. The trachea is much inflamed and the main bronchi have a circumference of 4 cm. below the first division. The bronchi in the greater part of the lung are not very greatly dilated, but have thickened walls. Toward the periphery of lungs, however, the smaller bronchi are dilated into spindle-shaped enlargements like beads on a necklace. These bronchi are dark red and apparently eroded. The bronchi to the upper lobes are less involved and cleaner than those below.

Microscopic examination shows numerous areas of bronchopneumonia tending to undergo necrosis in the centre. Necrosis frequently involves alveolar walls and adjacent bronchus. Considerable masses of bacteria and leukocytes may be seen in the central portions of these foci. Many bronchi are entirely eroded in places, the erosion extending to the alveoli, so that quite large cavities are formed, no trace of the bronchial wall remaining. In other parts the bronchi are only partly eroded and are very thin and dilated. The larger bronchi are not so extensively destroyed, showing merely desquamation of epithelium and infiltration of cells. The enormously enlarged bronchial lymph glands are œdematous, their sinuses filled with fluid, but not containing an excess of cells. The lymph cords are increased in bulk and the bloodvessels dilated. No areas of necrosis are present.

Permission for examination of the brain and spinal cord refused.

Cultures from contents of bronchi yielded bacillus influenzæ in great number with a few streptococci. From the washed and teased bronchial wall pure cultures of bacillus influenzæ were obtained, as also from the gangrenous areas. The lymph glands were sterile.

The bacterial masses above noted were seen in sections stained with methylene blue and eosin or with carbol thionin to consist almost entirely of tiny rods resembling the influenza bacillus. The infiltrating cells about the bronchial epithelium and extending down into the wall were frequently packed with these tiny rods. A few cocci and large bacilli were seen on the surface, but not deep in the tissues.

This case shows many of the features ascribed to acute influenza in the writings of Pfeiffer, Leichtenstern, Hitzig and others. The duration and slow development in this case would seem, however, to place it with the subacute or chronic cases. Here we have every reason to believe from cultural evidence during life and at postmortem that bacillus influenzæ was the principal if not the exclusive cause of the extensive pulmonary changes.

The case was in many ways clinically like a rapidly progressing phthisis, with the irregular fever and sweats, the loss of weight, and profuse expectoration and hemorrhage. Yet the daily examination of the sputum revealed no tubercle bacilli; and at autopsy the most careful search for tuberculous lesions, macroscopically and microscopically, was negative. The nervous features of the case strongly suggest the hemorrhagic encephalitis or "encephalitis grippalis" described by Leichtenstern, Königsdorf, Fürbringer, and others in association with influenzæ. In the absence of postmortem observations on the brain, however, the diagnosis can but be provisional. Prof. Osler suggested that brain abscess might account for these features of the case.

CASE II.—*Cough three years; worse in last year; large amount of foul sputum coughed up in paroxysms; emphysema; orthopnœa; no fever, chills, or sweats; no hemorrhages; bacillus influenzæ cultivated from sputum in practically pure culture; progressive weakening; steady increase in amount of expectoration; death; autopsy.*—B. G., male, white, aged forty-seven years, bookkeeper. Complains of "bronchitis." Admitted December 14, 1904. Died February 4, 1905.

Family History. Unimportant. No pulmonary disease.

Past History. Had scurvy in Africa with enlargement of liver; no pneumonia; no hæmoptysis; no night sweats; "severe catarrh" in 1893 and again in 1895; no other history suggesting influenza; habits good.

Present Illness. Began to cough three years ago. Worse last two years. Foul odor increasing and large quantities of sputum in paroxysms of coughing for a year past. Very severe paroxysms on rising, with evacuation of large amounts of sputum, greenish, purulent, rather thin and frothy. Paroxysms occurring several times a day and interfering with sleep at night. No hæmoptysis; no chills or sweats; no pain; has lost steadily in weight and strength in past year.

Physical Examination. Skin slightly cyanotic. Some clubbing of fingers. Chest rounded. Marked dyspnœa with activity of accessory muscles of respiration. Percussion note hyperresonant throughout chest, except in back, where there is slight impairment over left base and right interscapular region. Breath sounds everywhere well heard, and accompanied by numerous moist and piping rales. No tubular or amphoric breathing. No cavity made out. No friction rub. Blood count showed 4,600,000; erythrocytes, 9600; leukocytes and hæmoglobin of 87 per cent.

Bacillus influenzæ in very large numbers were cultivated from the sputum, with a very few colonies of diplococcus pneumoniæ. The patient did not respond to treatment and favorable surroundings. His cough continued severe and the amount of sputum large. There was never any elastic tissue found and daily examinations for tubercle bacilli were negative. The patient gradually lost strength, and was more and more exhausted by the coughing paroxysms necessitated by the profuse expectoration. He died February 24, 1905, without any acute exacerbation of his trouble.

Autopsy. Both lungs bound by old adhesions posteriorly. Bronchi contain a frothy turbid fluid with sickening odor. Lung substance emphysematous. No areas of consolidation. Bronchi everywhere dark red, granular-looking, and extremely and almost uniformly dilated to periphery of lungs. No special saccular dilatations or cavities. No tubercles.

Microscopically, there was general emphysema. Epithelial lining of bronchi well preserved in the main and showing scattered areas of metaplasia into a stratified squamous type with many mitoses. Marked infiltration of mucosa with lymphoid cells. The epithelial layer invaded by polymorphonuclear leukocytes. Hyperplasia of peribronchial lymph follicles. Atrophy of muscular coat and increase of the peribronchial connective tissue, including in places atelectatic alveoli with cubical epithelium. No evidence of tuberculosis. Owing to the fact that the lungs were injected with formalin *in situ*, it was impossible to secure cultures from the tissues at autopsy.

Stained sections, as in the previous case, however, showed that the walls of the bronchi were infiltrated with leukocytes, containing great numbers of small bacilli like bacillus influenzæ. Very few pneumococci were found in the sections stained by Gram's method. Coarse non-Gram staining rods were found in the masses of secretion in the bronchial lumen. The intracellular organisms were all of the influenza type.

CASE III.—*Chronic cough for thirty years; acute influenza eleven years ago with increased paroxysmal cough and profuse expectoration; signs of cavity in both lungs; no hæmoptysis; no tubercle bacilli; no elastic tissue; influenza bacilli in pure culture from sputum; clubbed fingers; arthritis deformans.*—S. N., single, white, female, aged forty-nine years, seamstress. First admitted in June, 1899. Complained of cough and profuse expectoration.

Family History. Good; no tuberculosis.

Past History. Subject to colds and winter coughs from girlhood. Measles the only acute disease of childhood. "Rheumatism" for seven years past, with gradual stiffening of fingers, shoulders, knees, and hips. In 1894 patient had severe attack of la grippe, since which time cough has been worse and expectoration more profuse. No night sweats; no hæmoptysis.

Present Illness. Really dates years back, a history of chronic paroxysmal cough with exacerbations every winter. Sputum abundant, tenacious, greenish, foul.

Physical Examination. A thin, poorly-nourished woman. Well-marked arthritis deformans, involving both knees and elbows; slight involvement of shoulder-joints.

Lungs. Signs of diffuse bronchitis over both fronts. Distinct signs of cavity in both interscapular regions; signs varying before and after paroxysms of cough and expectoration. Numerous moist and sonorous rales throughout both backs and axillæ. No fever; no sweats. Daily examination of sputum negative for tubercle bacilli and elastic tissue.

Second Admission, January 18, 1905. Complaint "cough." Arthritis more marked, involving nearly all the joints to a greater or less extent. Well-marked spondylitis. Cavity signs (amphoric breathing, pectoriloquy, cracked-pot sound, etc.), definite in both interscapular regions where previously noted. Diffuse moist sonorous rales. Large amount of fetid sputum. No hæmoptysis. Bacillus influenzæ in enormous numbers cultivated from sputum. Also small numbers of pneumococci. Sputum constantly negative for tubercle bacilli and elastic tissue.

Cultures from joint fluids negative on all media.

CASE IV. *Twelve years' standing; acute onset; probable empyema; early cavity formation; thickened pleura; paroxysmal cough; profuse foul expectoration; severe recurrent hemorrhages for ten years past; marked scoliosis; extreme hypertrophic osteoarthropathy; exacerbations often attended by fever and sweats; no tubercle bacilli; no elastic tissue; influenza bacilli in sputum in great number and pure culture.* —H. H., white, male, aged twenty-nine years, baker.

Family History. Unimportant; no tuberculosis..

Past History. Always strong and well until onset of present illness. Never any pulmonary disease. Habits good. Hands and feet unusually large from babyhood. In December, 1893, patient had severe cold after exposure; pain in right side; chills and fever; cough; night sweats. Profuse greenish expectoration; never blood-tinged. In bed two months. After patient was up and about for two weeks he began to have severe paroxysms of cough in the morning, bringing up large amounts of yellowish-green sputum, rather sweetish and sickening, probably due to the discharge of an empyema through the lung. This paroxysmal cough persisted, and fifteen months later the patient had his first hemorrhage from the lungs and was admitted to the hospital in March, 1895.

On this admission the patient was emaciated and very pale. Great enlargement of bones of hands, feet, and forearms. Right shoulder lower than left. Right chest rather flat above. Left lung clear, except for scattered rales. Right side shows definite signs of much thickened pleura below fifth rib and suggestion of cavity at angle of scapula. Sputum abundant, bloody. No tubercle bacilli or elastic tissue.

In the ten years following the patient was readmitted sixteen times, on nearly every occasion for severe hemorrhage from the lungs. The deformity of chest and right lateral scoliosis became more marked. Signs of cavity quite definite in right scapular region. Densely thickened pleura on right side. Diffuse rales on left. Osteoarthropathy more marked. Patient had persistent paroxysmal cough and profuse expectoration, rather fluid and purulent, very foul at times. Fever and sweats in the periods of exacerbation. Between these more severe attacks patient able to work at his trade. Patient responded well to treatment (rest, good food, etc.), cough becoming much less frequent and sputum greatly diminished in amount. There was always at least one paroxysm in a day, however.

Last admission, February, 1905. Condition practically unchanged except for a dry pleurisy on left side. Influenza bacilli were obtained in absolutely pure culture from sputum and in enormous numbers at first. As patient's condition improved the number of bacteria greatly decreased, though there were always a few to be found. In the ten years' observation there was never any elastic tissue found nor any tubercle bacilli.

Intratracheal injections were particularly beneficial to this patient, causing rapid diminution in amount of sputum and great reduction in number of bacteria, a 10 per cent. suspension of iodoform in olive oil being used for this purpose.

CASE V.—*Cough for nine years; history of pneumonia; empyema; operation; contraction of pleura; gradual development of paroxysmal cough with profuse, very foul expectoration; right lateral scoliosis; exacerbations with fever and sweats; no hæmoptysis; no tubercle bacilli; pneumococcus from sputum with small proportion of influenza bacilli and a fetor-producing organism; operation for drainage of cavity.*—R. S., white, female, aged fifteen years, school-girl.

Family History. Unimportant.

Past History. No illness other than chickenpox till an attack of pneumonia (right side) at age of six years, followed after twelve weeks by empyema and operation. Since this time patient has had a chronic paroxysmal cough with profuse, very foul expectoration, worse in winter, often prostrating her. Never any hæmoptysis. On first admission, October, 1899, patient was found to have definite signs of cavity in posterior and upper part of right lower lobe, there being a very noticeable intensification of the signs after the paroxysms of coughing. Left side clear, except for a few coarse rales. Some clubbing of fingers. Well-marked scoliosis to right. Sputum very profuse, very foul, of a greenish color. No tubercle bacilli or elastic tissue found. In the succeeding six years the patient was frequently readmitted with exacerbations of cough and expectoration, usually with some fever and occasional sweats; cavity signs in right lung persisting. She developed quite well, despite her infirmity. The cough and fetor were very distressing, however.

Last admission, January 19, 1905. Physical signs unchanged. Cough very distressing. Sputum from 200 to 400 c.c. in twenty-four hours. Influenza bacilli constantly present in sputum, but in small numbers, both on coverslips and in cultures. Pneumococcus in much greater preponderance. There was also isolated on one occasion a small micrococcus, which decolorized by Gram's method and grew only on blood-containing solid media, as will be noted later.

Patient was transferred to the surgical side and operation for drainage of the cavity in right lung was performed on May 23, 1905, by Dr. J. C. Bloodgood. Several ribs were resected and the lung exposed over the area of cavernous breathing. The lung was very atelectatic and dark red-like liver. Several small cavities were incised and drained. Patient is doing well two weeks after operation. Cultures from the contents of the cavities at operation yielded pneumococcus in great preponderance, with a few colonies of bacillus influenzæ. The surgical and pathological aspects of the case will be more fully reported by Dr. Bloodgood.

In addition to the above five definite cases of bronchiectasis there were two others of chronic bronchitis with probable dilatation of bronchi, from both of which influenza bacilli were obtained in absolutely pure culture. Both were men in middle life; had history of cough and profuse expectoration for years, worse in winter. Often fever and rarely night sweats. .No hæmoptysis. In neither case could any tubercle bacilli be demonstrated by daily examinations.

A sixth case which has a bearing on the pathogenicity of bacillus influenzæ as found in the sputum in chronic cases will complete the list.

CASE VI. *Chronic bronchitis thirty years; slight hæmoptysis; localized pleurisy with encapsulated effusion; bacillus influenzæ in pure culture from sputum; two weeks later empyema with bacillus influenzæ in pure culture from pus; operation; recovery.*—A. B., male, white, aged sixty years, tailor.

Family History. Negative.

Past History. Always healthy, except for chronic cough, worse in winter. No history of any acute pulmonary disease preceding.

Present Illness. In the winter of 1904 the patient had a severe attack of bronchitis; spat a little blood; occasional fever and sweats.

Rather profuse expectoration. Never quite well since. Four weeks ago became much worse, pain in side, night sweats, hæmoptysis slight.

Physical Examination. Diffuse bronchitis. Slight movable dullness in lower left axilla and back; irregular fever and sweats. Small amount of fluid, straw-colored, obtained by aspiration. Cultures on ordinary media sterile. Septum abundant, tenacious, mucopurulent blood-streaked. Cultures from sputum on March 6th yielded bacillus influenzæ in absolutely pure culture. Patient discharged on request March 12th, not much better. Readmitted March 30th in practically same condition, though feebler and with more fever and drenching sweats. Moderate leukocytosis. Signs of pleural effusion. Small amounts of slightly bloody fluid aspirated on several occasions. This was, unfortunately, not saved for cultures. On April 11th a few cubic centimetres of pus obtained by aspiration and from this influenza bacilli grew in absolutely pure culture. Patient transferred to surgical side. Eighth rib resected and pleura found very thick. A considerable amount of grayish, odorless pus evacuated and cavity drained. Patient improved rapidly.

The bacillus of Pfeiffer seems to have been the direct cause of the empyema in this case, the sputum having yielded absolutely pure cultures of this organism for some time previous to the onset of the empyema, and the same organism, and it alone, being found in the pus from the pleura at operation by culture and cover-slips.

CULTURAL METHODS. The sputum was collected in sterile cups and examined without delay. The washing method employed was substantially that described by Kitasato and by Lord. It was interesting to observe the striking difference in the bacteria found on coverslips made before and after washing. These were stained by Gram with bismarck brown counterstain in exactly the same way. While those made before washing showed usually a greater or less number of extracellular organisms (diplococci, streptococci, and other mouth bacteria), in addition to bacillus influenzæ, it was quite possible in most cases to wash the sputum so that the particles now showed only influenza bacilli, and these all intracellular. Pigeon-blood agar was used in most cases as a culture medium; in others sterile fetal blood from the placenta was added to the agar. On this latter medium it was interesting to note that involution forms appeared earlier and in much greater number than when pigeon, rabbit, or adult human blood was used. Some of these forms were so large and irregular as to give at first the impression of a mixed infection. Transfers to fresh media and control cultures of the same size and source on other blood media, however, produced in every case a pure typical growth of bacillus influenzæ. The gross appearance of the colonies on the fetal-blood agar was not different from that on the other tubes, being always the tiny, water-clear, discrete colonies, exactly as described by Pfeiffer. The small Gram decolorizing micrococcus isolated from Case VI. has not been identified accurately. It grew only on solid media containing blood. It decreased rapidly in vitality, so that it was lost after the fifth or sixth transfer. Its most striking characteristic was the production on the blood plates of the intense sickening sweetish fetor common in bronchiectasis. In some respects it conforms to micrococcus catarrhalis though that organism grows on ordinary media, and I have been unable to find any reference to its production of fetor when grown upon blood agar. None of the other organisms grown from the sputum in these cases (bacillus influenzæ, streptococcus, or pneumococcus) produced any fetor in pure or mixed cultures on like media.

Conclusions. 1. The influenza bacillus is probably capable of producing extensive pathological changes in the lungs, leading at times to bronchiectasis (Cases I. and IV.). The organism may be a secondary invader or associated with other bacteria; the latter may be the preponderant factor. In our small series there was no clinical difference determinable between the pure influenza infections and the mixed or non-influenza cases.

2. The very close clinical resemblance of these cases of bronchiectasis to some cases of chronic tuberculosis with cavity formation is important, and may, in the absence of cultural investigations, lead to wrong diagnoses. Physical signs alone, therefore, cannot be relied upon for a positive diagnosis of tuberculosis.

3. Care should be taken to prevent the possible infection of others from these chronic cases having influenza bacilli in the sputum, as the organisms may not have lost their pathogenicity by a continued growth in these old infections.

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N. B.—Since the completion of this investigation. and while waiting for surgical interference in Case V., a second admirable and comprehensive paper has appeared by Dr. Lord (Boston Medical and Surgical Journal, May 11 and 18, 1905), which covers a much wider field and greater experience. With his conclusions my smaller series seem fully to agree.